REMARKS

A. Claim Amendments

Claims 1, 3-22, and 24-29 are pending in the application. Claim 1 has been amended to incorporate a definition of "the at least one oxazolidinone antibacterial drug" using formula (I) and language incorporated from claim 2, cancelled herein. Claim 21 has been amended herein to incorporate a definition of "the at least one oxazolidinone antibacterial drug" term in that claim using formula (II) and language incorporated from claim 23, cancelled herein.

The present amendments have been introduced herein in order to facilitate prosecution of embodiments of the composition and method of the present invention, incorporating a particular class of oxazolidinone antibiotic drugs. However, Applicants respectfully reserve the right to prosecute broader claims directed to other embodiments of the present invention, or to prosecute the original set of claims, in a continuation or divisional of the present application.

B. Claim Rejections Under 35 U.S.C. § 102

The Manual of Patent Examining Procedure, 8th ed., August 2001 (hereinafter, "MPEP"), section 2131 explains that for any claim to be unpatentable, under 35 U.S.C. §102, over any single prior art reference:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claims of the present application have been rejected under § 102 for anticipation over each of three different references, discussed separately below. For reasons set forth below and in the Pena Declaration, submitted herewith, Applicants respectfully submit that each of the references fails to describe at least one element of each of the rejected claims.

1. Claims 1, 4, 7-9, and 15 Rejected Under § 102(b) for Anticipation by Maillard (US Pat No. 3,721,675). Maillard was cited as teaching a "suppository composition comprising an oxazolidinone antibacterial agent and lipophilic carrier," along

with "the concentrations of the claimed invention as well. (Office Action, p. 2, point 2, citing Maillard, Example 21).

Applicants respectfully submit that Maillard fails to teach the at least one oxazolidinone antibiotic drug element of claim 1, after amendment herein. All of claims 4 and 7-9 depend directly or indirectly from claim 1 and, therefore, inherently include all the elements and limitations of claim 1. Maillard teaches various compositions, including a suppository composition, of species of a particular class of oxazolidin-2-one derivatives, derivatives of 5-(piperidine-4-siro)-oxazolidin-2-one defined by Formula (I) of that patent. (See Maillard, column 1, lines 10-23). None of the compounds of Formula (I) of Maillard is an oxazolidinone antibiotic drug, as defined by formula (I) of claim 1 of the present application, after amendment herein.

In addition to the structural differences noted above, in paragraph 11 of the Pena Declaration, Dr. Pena notes that the class of oxazolidin-2-one derivatives of Maillard are not even described as being antibiotics. They are described, instead, as being useful as "analgesic and hypotensive drugs" (Pena Declaration, paragraph 11, citing Maillard, Abstract and col. 1, lines 40-42).

In view of the above, therefore, Applicants respectfully submit that Maillard fails to teach at least one element of claims 1, 4, and 7-9 of the present application, the "at least one oxazolidinone antibiotic drug" element. Therefore, Applicants respectfully submit that the rejection of claims 1, 4, and 7-9, under 35 U.S.C. § 102(b) over Maillard has been overcome. Applicants, therefore, respectfully request that this rejection be withdrawn.

2. Claims 1, 4, 8-10, and 15 Rejected Under § 102(b) for Anticipation by Borgulya *et al.* (US Pat No. 5,574,055). Borgulya *et al.* was cited as teaching a "suppository composition comprising an oxazolidinone antibacterial agent and lipophilic carrier," along with the dosage forms and dosage weights and concentrations of the present invention. (Office Action, p. 2, point 2).

Applicant respectfully submits that, like Maillard, Borgulya *et al.* fails to disclose the "at least one oxazolidinone antibiotic drug" of the claims of the present invention, after amendment herein. Borgulya *et al.* describes a specific class of oxazolidin-2-one derivatives, defined by Formula I of that patent, beginning on column 2, line 8. Formula I

of Borgulya *et al.* does not include any "oxazolidinone antibiotic drug", as defined by formula (I) of claim 1 of the present application, after amendment. These structural differences are also noted in the Pena Declaration, at paragraph 11.

In addition to the structural differences noted above, Applicants submit that the class of oxazolidin-2-one derivatives of Borgulya *et al.* are not even described in that reference as being antibiotics. They are described, instead, as being useful for the "control or prevention of depressive states, panic and anxiety states, cognitive disorders and neurogenerative diseases such as Parkinson's disease and Alzheimer's disease." (col. 1, lines 61-65). For further discussion of the structural and functional differences between the class of oxazolidin-one derivatives disclosed by Borgulya *et al.* and the at least one oxazolidinone antibiotic drug of formula (I) of claim 1 of the present application, see the Pena Declaration, at paragraph 11.

Claims 4, 8-10, and 15 depend from claim 1, and inherently include all the elements of claim 1, including the definition of "at least one oxazolidinone antibiotic drug" of formula (I), after amendment herein. For reasons set forth above, Applicants respectfully submit that Borgulya *et al.* fails to disclose at least that particular element of the claims. In view of the above, Applicants respectfully submit that the rejection of claims 1, 4, 8-10, and 15, under 35 U.S.C. § 102(b) over Borgulya *et al.* has been overcome. Applicants, therefore, respectfully request that this rejection be withdrawn.

3. Claims 1, 4, 5, and 10-14 were Rejected Under 35 U.S.C. §102(b) for Anticipation by Kaplan *et al.* (U.S. Pat. No. 4,727,070). Kaplan *et al.* was cited as teaching a suppository dosage form comprising an oxazolidinone agent and a hard fat, such as Witepsol H-15, as a carrier. (col. 4, lines 18-21, and Example 7).

Applicants respectfully submit that Kaplan *et al.* discloses a specific genus of antibiotics, a class of cephem compounds that contain an additional heterocyclic ring in the 7-position. All the cephem compounds of Kaplan *et al.* are derivatives of the cephalosporin antibiotic 7-[D-2-amino-2-(4-hydroxyphenyl)acetamido]-3-[(Z)-1-propenyl]ceph-3-em-4-carboxylic acid (BMY-28100). (Kaplan *et al.*, col. 1, lines 6-12). Kaplan *et al.* indicates that pharmaceutically acceptable metal and amine salts of the cephalsporin antibiotic described above convert to insoluble oxazolidinones in the

presence of a strong aqueous acid, at pH≤1. (*Id.*, lines 17-21, cited in Office Action, p. 3, item 4). However, the structure of the oxazolidinones is never defined; nor, is there any indication that the oxazolidinones would have antibiotic activity. Applicants respectfully submit that Kaplan *et al.* fails to disclose the "at least one oxazolidinone antibiotic drug" element of formula (I) of claim 1 of the present application, after amendment. (See, also, paragraph 9 of Pena Declaration). Claims 4 and 10-14 of the present application each depend directly or indirectly from claim 1 and, therefore, inherently include that particular element.

Applicants also respectfully submit that the suppository disclosed in Example 7 of Kaplan *et al.* does not comprise an oxazolidinone agent and a hard fat as a carrier, as indicated on page 8, item 4 of the Office Action. As is noted in paragraph 10 of the Pena Declaration, Example 7 of Kaplan *et al.* discloses: "a suppository dosage form of sodium 7-[2,2-dimethyl-4-(4-hydroxyphenyl)-5-oxo-1-imidazolinyl]-3-[(Z)-1-propenyl]-ceph-3-em-4-carboxylate monohydrate, an imidazolidinone derivative of the cephlosporin antibiotic, not an oxazolidinone, much less the oxazolidinone antibiotic drug of formula I of the present invention. (Kaplan *et al.*, col 10, lines 1-3)." See Pena Declaration, paragraph 10 for a more detailed discussion of the teachings of Example 7 of that reference.

For reasons set forth above, Applicants respectfully submit that Kaplan *et al.* fails to teach at least the "oxazolidinone antibiotic drug" element of claim 1 of the present application, after amendment. Claims 4 and 10-14 depend from claim 1, and therefore include all of the elements of claim 1. Applicants respectfully submit that the rejection of claims 1, 4, and 10-14, under 35 U.S.C. § 102(b) over Kaplan *et al.* has been overcome herein. Applicants, therefore, respectfully request that this rejection be withdrawn.

B. Claim Rejection Under 35 U.S.C. §103

Claims 1-29 were rejected under 35 U.S.C. §103(a) as being unpatentable over Maillard *et al.*, Borgulya *et al.*, and Kaplan *et al.* all in view of Barbachyn *et al.* (U.S. Pat. No. 5,574,055), "Linezolid" (*Drugs of the Future* 21(1): 116-1123, XP 000654643 (1996)), and Miyauchi (U.S. Pat. No. 4,900,730). The Office Action stated that the first

three references cited above "anticipate many essential elements of the invention"; but fail to disclose the specific oxazolidinone formulation recited by claims 2 and 18. Applicants respectfully note that the specific oxazolidinone formulation originally recited in claim 2, formula (I), has now been incorporated into claim 1 by amendment herein. Formula (I) of what is now claim 1 is identical to formula (II), formerly of claim 23, now incorporated into claim 21 and used to define the same term therein. Claims 3-20 all depend directly or indirectly from claim 1, while claims 22 and 24-29 all depend from claim 21.

Barbachyn *et al.* is cited in the Office Action as disclosing the oxazolidinone formula of claims 2 and 18, and *Linezolid* is cited as disclosing another general oxazolidinone formulation of the invention, as originally claimed. Miyauchi is cited as disclosing a rectal suppository where the active antibacterial agents are "micronized from 1-50 microns, and dissolved in the hard fat Witepsol H-15." (Office Action, citing Miyauchi, col. 5-24 and Examples).

1. *Prima Facie* Case Not Established - At Least One Element Missing

The MPEP states that:

> "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)." MPEP 2143.03.

Applicants respectfully submit that when the six references cited in the Office Action are viewed together, fail to teach or suggest at least one element common to the only independent claims of the present application, claims 1 and 21. The language common to each of the two independent claims includes the following: "an at least one oxazolidinone antibacterial drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone is poorly soluble, said composition being adapted for rectal administration..." (emphasis added). As noted above, the term "at least one oxazolidinone antibacterial drug" is defined in terms of formula (I) in claim 1, and in terms of formula (II) in claim 21, after amendment herein.

Even if one assumes that one of ordinary skill in the art of the present invention would have been somehow motivated to combine the teachings of each of the references cited above, Applicant respectfully submits that the combined teachings of the references fail to teach or suggest all the element(s) of the present invention, including the element(s) from the language of claims 1 and 21 highlighted above. Maillard, Borbulya *et al.*, and Kaplan *et al.* each disclose rectal formulations of various active agents. However, as noted in the preceding section, none of the three references discloses the oxazolidinone antibiotic agent element of formula (I) of claim 1, after amendment herein. In paragraph 12 of the Pena Declaration, Dr. Pena indicates that the specific classes of compounds disclosed by those three references were so structurally and functionally different as not to "have been likely to motivate one of skill in the art of the present invention to substitute any oxazolidinone antibiotic drug of formula (I) or of formula (II) of amended claims 1 or 21, respectively, of the present application, for the structurally and functionally dissimilar drugs in the rectal formulations of any of the three references."

As noted above, the Office Action cited Barbachyn *et* al., both for disclosing the specific formulation for an "oxazolidinone antibiotic drug" now incorporated into claim 5, and for stating that a suppository formulation of such compounds could be made. (Office Action, p. 5, citing Barbachyn *et al.* Abstract and col. 6, lines 49-55). Dr. Pena states, furthermore, that Barbachyn *et al.*:

> "fails to suggest that one could make a pharmaceutical composition suitable for rectal administration, "comprising at least one oxazolidinone antibiotic drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone antibiotic drug is poorly soluble ..." (Language common to claims 1 and 21, cited in paragraph 6, above, emphasis added.) Specifically, at no point does Barbachyn *et al.* teach or suggest the formation of a dispersion of solid particles of any oxazolidinone antibiotic drug in any medium in which the drug is poorly soluble." Pena Declaration, paragraph 13.

Dr. Pena goes on to note, in paragraph 14 of the Pena Declaration, that the "Linezolid" reference: "does not even disclose a rectal formulation of any oxazolidinone antibiotic drug, much less suggest the pharmaceutical composition of the present

invention, even when combined with all the references discussed above." (Citing the same five references discussed herein, immediately above.)

Finally Dr. Pena notes that Miyauchi discloses a long list of drugs suitable for rectal suppository formulations, where the active antibacterial agents are micronized and dissolved in the hard fat Witepsol H-15. However, she goes on to state that:

> "At no point does this reference suggest a pharmaceutical composition comprising a suspension of any antibiotic drug in a solid particulate form dispersed in a carrier in which the drug is poorly soluble, much less an oxazolidinone antibiotic drug of formula (I) or (II) of the present claims." Pena Declaration, paragraph 15.

For reasons set forth above, Applicants respectfully submit that a *prima facie* case of obviousness has not been established against claims 1 or 21, or against any of the present pending claims that depend therefrom, i.e. claims 3-20, 22, and 24-29. Therefore, Applicants respectfully traverse this rejection and request that it be withdrawn.

2. Surprising and Unexpected Results

In the alternative, even if a *prima facie* case of obviousness is somehow found to be established, Applicants respectfully submit that any such case is rebutted by evidence of surprising and unexpected results set forth in the specification of the present application, and in the Pena Declaration, submitted herewith.

As noted in MPEP 716.01(a), evidence of unexpected results is considered objective evidence of non-obviousness, and must be considered when present:

> "Affidavits or declarations containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc, must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103.
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> Examiners must consider comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F.2d 1029, 228 USPQ 940 (Fed. Cir. 1986)."

The Pena Declaration states that: "it would have been unexpected at the time the present invention was made for one to be able to produce a pharmaceutical composition of the present invention, a composition adapted for rectal administration." Pena Declaration,

paragraph 16. The Pena Declaration goes on to discuss the results of studies described in Examples 2 and 5 of the specification of the application. See Pena Declaration, paragraphs 17 and 18. In Example 2, dogs were rectally administered suppositories of linezolid dissolved in polyethylene glycol 4000, suppositories containing an amount of linezolid close to the solubility limit of linezolid in the carrier medium. In Example 5, dogs were rectally administered suppositories each containing 200 mg of linezolid in solid particulate form dispersed in a hard fat, Witepsol H-32, in which the drug is poorly soluble. The linezolid in the suppositories in Example 5 was not expected to be suitable for rectal administration, because of its poor solubility in the hard fat. However, surprisingly, the dogs rectally administered the suppositories in Example 5 had at least 10 times more linezolid in their blood plasma at every time point tested, compared to those tested in Example 2. (Pena Declaration, paragraph 18).

Dr. Pena noted that at the time the present claimed invention was made, one would not have expected such results of a pharmaceutical composition comprising an oxazolidinone antibiotic drug of formula (I), as described in claim 1 of the present application, for the following reasons:

> "It was considered a general rule at the time the present invention was made that unless a drug is either present in dissolved form in the carrier of a rectal formulation or dissolves therein, it cannot be absorbed upon rectal administration. Nothing about the oxazolidinone antibacterial drug of formula (I) of amended claim 1 of the present application indicated that any such drug would be an exception to this general rule. In fact, linezolid was known to be poorly soluble in most lipophilic carriers, at the time the present invention was made." Pena Declaration, paragraph 19.

Dr. Pena went on to note that, in view of this general rule, it was surprising and unexpected to find that rectal formulations of the present invention, such as those described in Example 5, were suitable for delivery of the oxazolidinone antibacterial drug, linezolid in this case, to the subjects to which they were rectally administered. See Pena Declaration, paragraph 20.

Finally, Page 3 of the specification also discusses surprising and unexpected consequences of the pharmaceutical composition of the present invention. These

surprising and unexpected effects were described in paragraph 21 of the Pena Declaration, where Dr. Pena noted that the pharmaceutical composition of the present invention:

> "allows for a smaller volume of the composition to be administered for a given dose; because, active agent loading is not limited by solubility in the carrier." (Specification, p. 3, lines 25-27). It also "makes the administration more practical and convenient to the subject," something particularly important where "the maximum tolerable volume of administration is small." (*Id.*, lines 27-30)

In view of the objective evidence of surprising and unexpected results set forth in the present specification and in the Pena Declaration, as discussed hereinabove, Applicants respectfully traverse the rejection of claims 1, 3-22, and 24-29, under 35 U.S.C. §103(b) in view of the six references cited above.

SUMMARY

For reasons given above, Applicants respectfully submit that all of the claims remaining pending in the present case (i.e., claims 1, 3-22, and 24-29) are in condition for allowance. Issuance of all the claims is, therefore, requested. The Examiner is invited to contact the undersigned at the telephone number given below, should he wish to discuss the present amendment and suggest changes to the claims in order to further prosecution of the application.

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